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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20857

RE: Docket No. 1998D-0266
Draft Guidance on Current Good Manufacturing Practice for Positron Emission Tomography Drug Products; Availability [70 **Federal Register** 55145]

Dear Sir/Madam:

The Society of Nuclear Medicine (SNM) appreciates the opportunity to provide the attached comments on the Draft Guidance for Current Good Manufacturing Practice for Position Emission Tomography Drugs (21 CFR Part 212) as published in the September 20th *Federal Register*.

The SNM on behalf of its membership acknowledges the significant effort that the FDA has put into the regulation and guidance documents for PET Drug Product CGMPs. These documents represent the outcome of many years of interaction between the FDA and the PET community. Many of the written responses and comments from the public meetings have been incorporated into the proposed rule and guidance documentation. As documented in this response we have identified a few sections of the document that require clarification or revision.

We look forward to continuing the open dialog with the FDA with regards to the regulation of PET Drug Products. Please feel free to contact Hugh Cannon at the SNM (703.708.9000) or any of the members of the working group if you have any questions regarding our response.

Sincerely,

SNM CGMP Working Group

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Titles of the proposed rule and draft guidance:

We direct the Agency's attention to inconsistencies in the titles of the proposed rule and the draft guidance. Specifically, we note that the title of the draft 21 CFR Part 212 refers to "Positron Emission Tomography *Drugs*," while the title of the draft guidance refers to "PET *Drug Products*." We suggest for sake of clarity and consistency that these titles be consistent with the definitions for "PET Drugs" and "PET Drug Products" as defined in the proposed rule.

Recommendation:

We recommend that the title of the final rule be changed to "Current Good Manufacturing Practice for Positron Emission Tomography Drug *Products*."

Section V.A Regulatory Requirements:

This section describes the activities of the quality assurance function as set forth in the proposed rule at §212.20. In the draft guidance, at line 286 (p7), it states, "Ensure that *all* errors are investigated and corrective action is taken." The requirement for *all* errors to be investigated is inconsistent with the proposed rule at §212.20(d) which states, "If errors have occurred, or a production batch or any component of the batch fails to meet any of its specifications, you must *determine the need for an investigation, conduct investigations when necessary*, and take appropriate corrective actions." The statements in the draft guidance are inconsistent with the requirements in the proposed rule.

Recommendation:

We recommend that the language on line 286 in the draft guidance be revised to – "Ensure that all errors are reviewed. When it is determined that an investigation is appropriate, document the investigation and corrective action(s) taken."

VII.B.4.a Control of components, containers and closures, acceptance testing:

Lines 694 – 700 of the draft guidance allow the acceptance of reagents, solvents, gases, purification columns, and other auxiliary materials provided that they meet internal written specifications and that a COA is obtained and examined. We specifically note the absence of commercially prepared microbial growth media from the list of examples.

Commercially prepared growth media is provided with a manufacturer's Certificate of Growth Promotion and is labeled by the manufacturer with a conservative expiration date. Although the USP Chapter <71> on Sterility Tests requires a growth promotion test (GPT) every 90 days, we believe that commercially prepared growth media has been demonstrated to be reliable and robust when stored according to the labeled requirements and when used within its labeled expiration date. Retesting of commercially prepared growth media for GPT should not be required because it would pose an enormous burden upon PET sites without benefit. It would not be feasible to send material to an outside laboratory for repeated testing as this would make it impossible to control inventories, and resultant additional exposure of the material to uncontrolled shipping conditions may further compound the interpretation and validity of the results to material retained for use. Additionally, and most importantly, to perform such testing internally, a PET drug

product manufacturer, especially those situated outside of a medical institution setting, would have to employ a microbiologist and have a separate and dedicated site for microbiological testing, which would be economically unfeasible. A requirement for GPT of a commercially prepared microbial growth media is inconsistent with the spirit of the other provisions of the CGMPs for PET drug products.

Recommendation:
We strongly recommend that commercially prepared growth media be added to the example list of materials in this section.

VIII.A. Production and Process Controls, Regulatory requirements:
This section describes the requirements for a batch production and control record as such a record is required under §212.50(c) of the proposed rule. Statements in the draft guidance regarding the nature of the batch production and control record are inconsistent with the description and list of requirements for such a record as presented in the proposed rule at §212.50(c), as follows:

- At line 778 it states, "Proposed §212.50(c) would require that a batch production record be generated from the master production record template for each new batch...."
- At line 799 it states, "The master production record serves as a template for all batch records....."
- However at line 853 it states, "The batch record is therefore a simplified version of the master production and control records that should contain the information needed for a documented history of the batch produced."

The first and second bulleted statements above are inaccurate with regard to §212.50(c). The third bulleted statement is consistent with the itemized requirements in the proposed rule.

Recommendation:
We recommend statements found on lines 778 and 799 in the draft guidance be revised so they are aligned and consistent with section §212.50(c) in the proposed rule as stated in line 853.

VIII.B.(6) Production and Process Controls, Records -

Since the format of a batch record can be either a paper or an electronic copy (as per line 851), the term "printout" on line 861 seems to refer only to the paper version of the documentation.

Recommendation:
We recommend the following changes at line 861 – "unit, the paper printout *or electronic record* at the end of synthesis documenting the execution of the production"

On line 864, please refer to the above noted rationale with regard to the following recommendation.

Recommendation:
We recommend the following changes at line 864 - A compilation of tests and paper printouts *or electronic record* that led to acceptance of the final product.

XI.B. Finished Drug Product Controls and Acceptance Criteria, Finished Product Testing:
This section expands on the requirements for finished product testing as stated in §212.70 of the proposed rule.

It is our understanding that the proposed rule is dedicated to PET Drug Products under an approved NDA. All investigational work being performed under RDRC and IND will be carried out under the guidance of USP <823>. This is inconsistent with the information in line 1187.

Recommendation:
We recommend that line 1187 be changed as follows: " recommend using approved NDA specifications. Under"

XI.B. Finished Drug Product Controls and Acceptance Criteria, Finished Product Testing:
This section expands on the requirements for finished product testing as stated in §212.70 of the proposed rule.

"Pursuant to and consistent with the current revision of the USP **General Notice, Test and Assays**, data derived from manufacturing *process validation* [verification studies] and from *in-process controls* may provide greater assurance that a batch meets a particular monograph requirement than analytical data derived from an examination of samples drawn from that batch. On the basis of such assurances, the analytical procedures in the monograph may be omitted by the manufacturer in judging compliance of the batch with the Pharmacopeial standards. An applicant who wishes to eliminate specific end product testing should provide adequate supporting data in a drug application."

Recommendation:
We recommend that the Agency insert the following paragraph at line 1191 -

"In accord with the current revision of the USP General Notice, Test and Assays, data derived from manufacturing process verification studies and from in-process

controls may provide greater assurance that a batch meets a particular monograph requirement than analytical data derived from an examination of samples drawn from that batch. On the basis of such assurances, the analytical procedures in the monograph may be omitted by the manufacturer in judging compliance of the batch with the Pharmacopeial standards. An applicant who wishes to eliminate specific end product testing or wishes to reduce the frequency of a test should provide adequate supporting data in a drug application."

XI.C Finished Drug Product Controls and Acceptance Criteria, Microbiological Tests for Sterile PET Dugs:

This section expands on the requirements for finished product testing as stated in §212.70(e) of the proposed rule.

Recommendation:

At line 1192, the wording in the heading of paragraph **"C"** should be changed from "Microbiological Tests for *Sterile PET Drugs*: to "Microbiological Tests for *Sterile PET Drug Products*." This would add consistency with the definition of "PET Drugs" and "PET Drug Products" as defined in the proposed rule.

The wording of the paragraph at line 1211 should be changed to read "*PET Drug Product*" rather than "*PET drug*."